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Serotonergic Influences on Food Intake: Effect of 5-Hydroxytryptophan on Parameters of Feeding Behaviour in Deprived and Free-Feeding Rats

J. E. BLUNDELL AND C. J. LATHAM[1]

Biopsychology Laboratories, Psychology Department, Leeds University, Leeds LS2 9JT, UK

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BLUNDELL, J. E. AND C. J. LATHAM. *Serotonergic influences on food intake: Effect of 5-hydroxytryptophan on parameters of feeding behaviour in deprived and free-feeding rats.* PHARMAC. BIOCHEM. BEHAV. 11(4) 431–437, 1979.—Three experiments were carried out to examine the effect of the serotonin precursor, 5-hydroxytryptophan, upon food intake and the micro-structure of eating in deprived rats, and on the pattern of meal taking in free-feeding animals. The study also investigated the capacity of a peripheral decarboxylase inhibitor (MK-486) to antagonise the effects of 5-HTP in order to identify a central or peripheral mode of action. In deprived rats 5-HTP brought about a dose related inhibition of food intake which was mildly antagonised by MK-486. A detailed analysis of the behavioural changes occurring during eating showed that the inhibition of food intake by 5-HTP was reflected in a reduced number of eating bouts and a slower rate of eating. MK-486 did not antagonise the effect of 5-HTP on eating rate. In free-feeding rats whose food consumption was continuously monitored for 24-hr periods, 5-HTP gave rise to a reduction in meal size and a slowing of the intra-meal rate of eating. These findings are in keeping with the effects of other serotonergic manipulations on the patterns of feeding in rats.

Serotonin 5-Hydroxytryptophan Feeding patterns Meal size Food intake Rate of eating

NUMEROUS reports have shown that the pharmacological manipulation of serotonin (5-HT) metabolism can bring about alterations in food intake (see [6,7] for review). These data do not provide direct evidence for a physiological role for 5-HT in the control of food consumption but merely demonstrate that alterations in food consumption arise as a consequence of experimental interventions believed to adjust the activity of serotonergic systems. However, it has also been shown that alterations in the availability of food can lead to adjustments in the metabolism of brain serotonin [30,38]. In addition, experiments involving micro-knife surgery of brain pathways and direct intra-cerebral injections have suggested that feeding may be partially controlled by interactions between dopamine and serotonin [34], noradrenaline and serotonin [32], or by interactions between all three amines [14]. In turn, the accumulation of evidence has led to various suggestions concerning the possible functions of 5-HT in feeding processes. For example, it has been suggested that serotonin systems may contribute to the day and night control of satiation [26], may modulate other systems regulating body weight [18], may regulate the intake of protein [2], or the relative proportions of protein and carbohydrate [22], or may control specific parameters of feeding behaviour [9,10]. Because of the theoretical and practical implications of these proposals [15], it seems important to examine further the effect of serotonergic manipulations on food consumption.

In general those manipulations believed to enhance the synthesis of serotonin or to facilitate 5-HT synaptic activity lead to a diminution in the amount of food consumed [6,7], at least over short periods of time [43,44]. In keeping with this proposal the precursor of serotonin, 5-hydroxytryptophan (5-HT) has been demonstrated to reduce food intake in food deprived rats [13,29]. Although there are limitations to the use of 5-HTP as an experimental device owing to its conversion to 5-HT in non-serotonergic neurons (e.g. [19]), this compound has been shown to reverse deficits brought about by low levels of 5-HTP [33] and has been used as an investigative tool in animal [27,35] and human [49] studies. However, the observation of a suppression of the weight of food consumed following the administration of a chemical to severely deprived rats may not be a particularly useful procedure for understanding the mechanisms controlling behaviour [17,36] or for investigating the effect of drugs upon feeding processes [10]. For this reason, the present study employed two procedures designed to reveal more detailed information concerning the effect of pharmacological manipulations on feeding behaviour. One procedure involved an

[1]Now Lecturer in Psychology, Psychology Department, Goldsmith's College, University of London, New Cross, London, SE14 6NW, UK.

examination of the micro-structural elements of feeding activity (e.g. [47,48]) and the second procedure embodied an analysis of meal parameters in free-feeding animals [39]. Both the micro-structure technique [9] and the meal pattern analysis [12] have been shown to be capable of sensitive discrimination between differing pharmacological manipulations.

In addition to considering the way in which the elements of feeding behaviour may be re-organised following 5-HTP administration, the mechanism of this action can also be questioned. For example, the neurotransmitter serotonin is located not only within the brain (e.g. [3]) but also in the periphery with large stores being found in the gut (e.g. [1]) where it may possibly influence the intensity of the signals arising from food consumption. Consequently, any suppression of food intake by 5-HTP may be mediated by either central or peripheral action. Indeed, it has recently been reported that certain behavioural effects of 5-HTP were due to changes in peripheral serotonergic systems [16]. The possibility of peripheral involvement may be examined by administering 5-HTP in conjunction with carbidopa (MK-486), a peripherally acting decarboxylase inhibitor [5]. It follows that if the suppressant effect of 5-HTP is mediated by peripheral adjustments then this action should be blocked by prior administration of MK-486. Accordingly, an initial parametric study was carried out to investigate the effect of MK-486 on the dose-response relationship for anorexia produced by 5-HTP.

EXPERIMENT 1

METHOD

Animals

Male hooded (Lister rats (280–310 g) were housed in single cages in a quiet environment with a 12-hr light dark cycle. For 10 days prior to the start of the experimental treatments the rats were exposed to a feeding cycle of 18 hr deprivation followed by free access to food for 32 hr. In addition the rats were handled daily and also received two sham intraperitoneal injections at times corresponding to subsequent drug administration. These procedures were adopted in order to acclimatise animals to all novel and stressful features of the experiment before the period of data collection.

Design and Procedure

The study conformed to a 3×4 factorial design which included four dose levels of 1-5-HTP (0, 30, 60 and 90 mg/kg) and 3 doses of MK-486 (0, 50 and 75 mg/kg). Each animal was tested once and received two injections prior to the start of the period of food intake measurement. One hour before the feeding test animals were given IP injections of MK-486 (or saline), and 30 min later 5-HTP or saline was administered.

At the start of the feeding period a weighed amount of food (diet 41B pellets) contained in small dishes was placed in the cages. Food intake was monitored periodically over 24 hr and measurements were taken after 1, 2, 4 and 24 hr. Spillage was collected on tissue paper placed beneath the wire mesh cage floor and weighings were made to the nearest 0.1 g.

The results were analysed by an analysis of variance procedure for single measures and where appropriate pairs of means were compared using Tukey's procedure.

RESULTS AND DISCUSSION

The effect of 5-HTP and MK-486 on the amount of food eaten during the first hour of the feeding period is shown in Fig. 1. The graph reveals that 5-HTP brought about a dose related suppression of food intake, and in keeping with this effect the analysis of variance showed a significant main effect for the precursor treatment, $F(3,60)=45.74$, $p<0.01$. The other main effect due to the MK-486 injections was not significant, $F(2,60)=0.59$, demonstrating that this treatment did not produce any systematic effect on food intake. Although MK-486 administered alone gave rise to a noticeable reduction in food intake (Fig. 1) this decrement was not significant (Tukey's procedure, critical value=4.2). However, the ANOVA revealed a significant interaction between the two main treatments, $F(6,60)=2.97$, $p<0.05$, indicating that pretreatment with MK-486 modified the action of 5-HTP on food consumption. Further analysis of this effect showed no significant differences between the means for MK-486 pretreatment at any dose of 5-HTP.

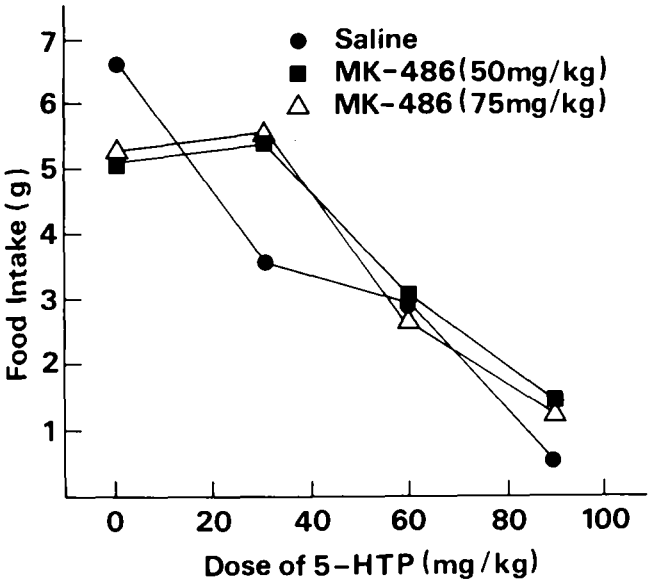

FIG. 1. Dose-response curves showing the effect of 5-HTP and MK-486 upon food intake measured during a 1-hr feeding test in deprived rats. Each point on the curves is the mean value for 6 rats. See text for statistical analysis.

The main effect due to 5-HTP was significant at all measuring periods, smallest F value $(3,60)=3.40$, $p<0.05$, whilst the main effect due to MK-486 was never significant. A further significant interaction was detected at the 0–4 hr measurement period, $F(6,60)=2.53$, $p<0.05$, but not at the 2 hr or 24 hr period.

These results have confirmed previous results showing that food intake is markedly reduced by injections of 5-HTP. However, pretreatment with the peripheral decarboxylase inhibition MK-486 modified the anorexic action of 5-HTP. This modification was not a massive effect but was obvious

TABLE 1

EFFECT OF FOUR TREATMENT CONDITIONS ON FOOD INTAKE AND CERTAIN PARAMETERS OF FEEDING BEHAVIOUR DERIVED FROM THE CONTINUOUS OBSERVATION OF RATS DURING A 1-HR FEEDING PERIOD. FIGURES IN THE BODY OF THE TABLE REPRESENT MEAN VALUES FROM 8 ANIMALS. SEE TEXT FOR STATISTICAL TREATMENT OF DATA.

Injection 1st	Injection 2nd	Food Intake (g)	Duration of eating (min)	Latency (min)	No. of eating bouts (N)	Local rate of eating (g/min)
Saline	Saline	9.5	33.9	0.4	28.2	0.28
Saline	5-HTP	6.1	31.3	1.2	13.6	0.19
MK-486	Saline	7.7	28.7	1.2	23.3	0.27
MK-486	5-HTP	6.7	34.1	1.6	26.2	0.20

as a lessening of the suppressant action of 5-HTP. The effect of 5-HTP on food intake was never completely eliminated by MK-486 but the partial antagonism suggests that at least some part of the anorexic action of 5-HTP may be mediated by peripheral changes. The following experiment was carried out to investigate whether the antagonistic action of MK-486 on 5-HTP would influence the alterations in the microstructure of eating brought about by serotonergic manipulation.

EXPERIMENT 2

METHOD

Animals

Hooded rats (345–370 g) were housed singly and kept under identical environmentul conditions.

Design and Procedure

The pre-experimental procedures employed to accustom animals to stressful techniques were similar to those previously described. However, this study conformed to a 2x2 repeated measures design in which each animal served as its own control and received each of the experimental treatments in turn. As in the first experiment, rats received two injections prior to each testing period. For the first injection, given 60 min before the test, rats received either 0.9% saline or 50 mg/kg MK-486. The second injection (30 min before the test) was of saline or 30 mg/kg l-5-HTP. Consequently, each rat received four different combinations of drug treatments and these were administered in a counterbalanced order according to two latin squares. A minimum period of 72-hr intervened between successive test sessions.

At the time of the first injection the animal's cage was removed from the rack and placed in a position where the rat's activities could be easily observed. Subsequently, during the first hour of the feeding test the rat's behaviour was continuously observed and recorded by a trained observer. The animal's activities were exhaustively classified into six categories—eating, drinking, locomotion, sedation, grooming and miscellaneous—and the observer recorded the onset, duration and termination of these behavioural events by depressing buttons on a control panel linked to a 6-channel event recorder. The data collected in this way were later processed to provide the following parameters of eating behaviour: latency to the onset of eating, total duration of time spent eating, number of separate bouts of eating, duration of eating bouts and the local rate of eating. This final measure refers to the rate at which each rat consumed food when in the act of eating, and should be distinguished from the overall rate which could be computed simply by dividing the amount of food consumed by the time allocated for the feeding test. The local rate of eating has previously been shown to be an extremely sensitive indicator of the effect of pharmacological manipulation on eating [9]. All of the observations in this experimental together with the computation of data were carried out under double blind conditions. Because of the considerable inter-animal variability on these detailed elements of feeding behaviour, the data were subjected to a square root tranformation before the analysis of variance was carried out.

RESULTS AND DISCUSSION

The effects of 5-HTP and MK-486 on the measured elements of feeding behaviour are set out in Table 1. As expected, the various pharmacological treatments produced a significant effect on the amount of food consumed with a highly significant main effect of the 5-HTP condition, $F(1,7)=16.9, p<0.01$. Although MK-486 again brought about a noticeable antagonism of 5-HTP anorexia, the interaction did not reach statistical significance, $F(1,7)=3.1$. The treatments did not produce statistically significant effects on the total amount of time spent eating, latency, the average duration of eating bouts or the number of eating bouts, maximum $F(1,7)=4.2$, although 5-HTP appeared to reduce the number of eating bouts compared with saline treatment and the MK-486/5-HTP combination. A significant main treatment effect was observed for the action of the 5-HTP condition on rate of eating, $F(1,7)=20.4$, $p<0.01$, but there was no effect of MK-486 on rate, $F(1,7)=0.12$, nor was the interaction significant, $F(1,7)=0.22$.

These results have shown that the reduction in food consumption brought about by injections of 5-HTP in a one hour feeding test is characterised by an apparent diminution in the number of separate bouts of eating and by a marked slowing of the rate of consumption. These effects are similar to those observed following the administration of other drugs such as fenfluramine and ORG-6582 which are known to influence the synaptic release and re-uptake of serotonin [9]. In addition the results have shown that although MK-486 gave rise to a mild antagonism of the anorexic effect of 5-HTP, this peripheral decarboxylase inhibitor exerted little or no effect on the local rate of eating. Consequently, to the

extent that MK-486 blocks the peripheral action of 5-HTP, the observed reduction in the local rate of eating appears to be centrally mediated.

This experiment has indicated that the suppression of food intake brought about by 5-HTP is mediated by pronounced alterations in the style of feeding behaviour displayed by the animal. These alterations are understandable in the light of behavioural changes induced by other serotonergic agents administered to deprived rats. Moreover, when pharmacological manipulation of serotonin metabolism has been carried out in free-feeding rats which have never been exposed to the rigours of food deprivation, reliable effects have been observed on meal patterns and intra-meal events. In order to further investigate the behavioural mechanisms underlying 5-HTP anorexia, the following experiment examined the effect of 5-HTP administration on the profile of meal-taking in non-deprived rats.

EXPERIMENT 3

METHOD

Animals

The subjects were eight male hooded rats (330–380 g) reared on a 12/12 hr light-dark cycle. The animals were housed singly and throughout the course of the experiment all testing was carried out in these home cages.

Design and Procedure

Each cage was placed in a temperature-controlled, sound-attenuating ventilated experimental chamber in order to minimise any modification of the animals' behavior due to disturbance in the laboratory environment. Food in the form of 45 mg precision pellets was available from a pellet-detecting eatometer located in each animal's home cage. Each eatometer consisted of a V-shaped trough in which a light source and photosensor were positioned at opposite ends of the base of the V. Normally a food pellet rested at the base of the V and occluded the photosensor. When the pellet was removed by the rat the light source activated the photosensor which in turn led to the delivery of the next pellet from a pellet dispenser.

The removal of a pellet from the trough of an eatometer activated the pellet dispenser associated with each eatometer and also resulted in a discrete pulse being sent to a NOVA 840 mini-computer. A data acquisition programme determined the source and the exact time of arrival of each pulse and these data were recorded on a floppy disc system. At the end of 24 hr of continuous monitoring the disc was changed. This system enabled the analysis of feeding patterns for each 24 hr period to proceed without interfering with the continuous monitoring function of the computer.

Data were analysed by a programme developed in our laboratories according to the following criteria. A meal was defined as the removal of 5 or more food pellets separated from any other number of 5 or more pellets by an interval of at least 15 min. In reality, this definition of a meal is quite conservative since it has been our experience of working with raw data from these animals under these conditions that meals are rarely less than 25 pellets (1.1 g) in size and are usually separated from each other by 30 min or more. In addition to determining the number of meals taken together with the duration (minutes) and size (grams) of each meal, the programme was designed to compute the rate of eating (g/min) within every meal. Moreover, since the beginning and end of each meal was precisely defined, the pre- and postmeal intervals were obviously known and from these data the satiety ratio (size of the meal compared with the duration of the postmeal interval) was computed. The criteria used in this study are consistent with those usually adopted by other researchers (e.g. [37]).

As in the previous experiments, animals were handled daily and received sham injections in order to fully accustom the rats to all aspects of the test procedure, prior to the onset of experimental treatments. At the end of this period of acclimatization any animals not displaying stable feeding patterns were removed from the experiment. Those animals which demonstrated stable temporal profiles of meal taking over several days entered the test phase during which treatments were administered. On any test day animals received an injection of 50 mg/kg MK-486 followed by 30 mg/kg l-5-HTP, or two sequentially administered control injections of 0.9% saline. Each animal served as its own control and received both treatments with 72 hr intervening between successive tests. The order of presentation of treatments was counterbalanced to avoid systematic ordering effects. Following each treatment, the animal's patterns of feeding were continuously monitored for 24 hr and from the data collected the computer programme determined the number and size of all meals taken, the overall amount of food consumed, the rate of eating within meals and the distribution of eating between the light and dark phases of the 24 hr cycle. This experiment was designed to examine the influence of a serotonin precursor upon the pattern of feeding and was not intended to directly assess the effect of MK-486 on the action of 5-HTP. The data from this experiment were analysed by an analysis of variance procedure for repeated measures regarding the treatments and phases of the light-dark cycle as separate factors.

RESULTS AND DISCUSSION

The results of this experiment are shown in Table 2. As expected a significant main effect was observed for the action of 5-HTP/MK-486 treatment on the weight of food consumed, $F(1,6)=14.6$, $p<0.01$. A significant phase effect was also obtained, $F(1,6)=8.5$, $p<0.05$, together with a significant treatment × phase interaction, $F(1,6)=6.94$, $p<0.05$. This interaction indicates that the treatment reduced food consumption more severely during the dark phase of the cycle, an understandable finding since the drugs were always administered immediately before the onset of the dark phase. The drug treatment did not produce any marked effect on the number of meals consumed although a significant main effect was observed for the phase factor, $F(1,6)=6.0$, $p<0.05$. In contrast, the 5-HTP treatment produced a significant effect on meal size, $F(1,6)=18.19$, $p<0.01$, which was apparent in both phases of the light-dark cycle and over the full 24 hr period. There was no significant effect of phase on meal size, $F(1,6)=4.62$, nor was the treatment × phase interaction significant, $F(1,6)=0.87$. This clear diminution in meal size brought about by 5-HTP was accompanied by a marked slowing of the rate of eating within meals, $F(1,6)=18.5$, $p<0.01$. There was no significant effect of phase on rate of eating, $F(1,6)=1.8$, and the treatment × phase interaction was non-significant, $F(1,6)=0.9$. A satiety ratio was computed for meals taken over the full 24 hr measure-

TABLE 2

EFFECT OF 5-HTP AND MK-486 ON AMOUNT OF FOOD CONSUMED (W), NUMBER OF MEALS (N), AVERAGE MEAL SIZE (MS) AND RATE OF EATING (R) IN FREE-FEEDING ANIMALS WHOSE FOOD INTAKE WAS CONTINUOUSLY MONITORED FOR 24 HR. VALUES GIVEN IN THE TABLE ARE MEANS ± SEs. FULL STATISTICAL DETAILS GIVEN IN TEXT.

Treatment	Monitoring period											
	0–24 hr				12 hr dark phase				12 hr light phase			
	W	N	MS	R	W	N	MS	R	W	N	MS	R
Saline	29.2	13.0	2.2	0.42	19.4	7.9	2.5	0.42	9.8	5.1	1.9	0.42
	±0.6	±1.7	±0.3	±0.02	±1.3	±1.1	±0.3	±0.02	±0.8	±0.9	±0.3	±0.03
MK-486 and 5-HTP	19.1	11.9	1.6	0.34	11.4	6.6	1.7	0.33	7.7	5.3	1.4	0.34
	±3.4	±1.4	±0.3	±0.02	±2.2	±0.8	±0.3	±0.02	±1.8	±1.0	±0.3	±0.02

ment period and revealed that treatment with 5-HTP reduced the ratio from 1.9:1 to 1.3:1. This means that 5-HTP tended to prolong the postmeal interval relative to the size of the meal. Although this effect was clearly apparent in 7 of the 8 animals, the difference between the means following control and experimental treatments just failed to reach a statistically significant value, $t(7)=2.27$, $p>0.05$.

GENERAL DISCUSSION

A number of previous studies (e.g. [13, 29, 42], together with Experiments 1 and 2 in the present series, have demonstrated that injections of 5-HTP reduce food consumption in rats subjected to a prior period of food deprivation. Experiment 3 reported above has revealed that 5-HTP administration leads to a restriction of food intake in free-feeding rats which have never been exposed to a deprivation regime. Moreover, the effect of 5-HTP in free-feeding rats was of greater intensity and was more long-lasting than in deprived animals. For example, in Experiment 1 a dose of 30 mg/kg 5-HTP (in conjunction with 50 mg/kg MK-486) reduced the mean food intake over a 24 hr period from 36.8 (±3.1) g to 35.1(±4.0) g—a nonsignificant reduction of only 3%. However, the results of experiment 3 show that in free-feeding rats the same treatment reduced food intake by more than 30%. A similar disparity between the strength of effect of a treatment in deprived and free-feeding rats has recently been demonstrated for typtophan [11], an agent which has previously been reported to exert no effect on food intake [4, 46]. These findings suggest that the free-feeding animal may constitute a more sensitive preparation than the deprived rat for the detection and characterization of the effects of drugs on feeding behaviour.

One of the considerations which prompted these experiments was the intention to further investigate the action of serotonergic manipulation on the pattern of food consumption. Although no independent measure of the effect of 5-HTP on serotonin metabolism was carried out, it is known from previous studies that doses of 5-HTP of the magnitude used in the present experiments reverse deficits brought about by low concentrations of brain serotonin [33] and also increase brain levels of serotonin for several hours after injection [24]. The administration of 5-HTP has, however, been reported to increase the brain concentration of noradrenaline measured 45 min after administration [41]. Consequently, it is possible that alterations in other neurotransmitter systems contributed to the behavioural changes observed in these experiments. However, a number of features run counter to this possibility. First, the effect of 5-HTP on meal size in free-feeding rats is quite consistent with the effect on meal patterns observed after the administration of various treatments known to influence serotonin metabolism. A significant reduction in meal size has been detected after treatment with fenfluramine [12,20] which is known to release serotonin and to block its reuptake (23], ORG-6582 [9] which blocks the uptake of serotonin [45] and tryptophan [31] which leads to an increase in the brain levels of serotonin (e.g. [21]). Second, an increase in the brain concentration of noradrenaline brought about by intraventricular injection leads to an increase in meal size [40], an effect opposite to that observed with serotonergic treatments. Third, in deprived rats 5-HTP gives rise to a marked slowing of the rate of eating quite similar to that observed after treatment with fenfluramine or with serotonin uptake blockers such as ORG 6582, FG-4963, and Lilly 110140. This action is opposite to the effect on eating rate observed after pharmacological treatment known to facilitate catecholaminergic transmission [9]. Consequently, a number of lines of evidence suggest that the observed effects of 5-HTP on meal size and the rate of eating are mediated by action upon serotonergic systems.

In keeping with the observed similarity between the effects of 5-HTP and fenfluramine on temperature [28], sleep [50] and conditioned responses [42] the present experiments have demonstrated similar effects of these two agents on a number of feeding parameters. If special consideration is given to the influence of these agents on meal size then the data may provide more evidence for the role of serotonergic processes in satiety (e.g. [8]). Alternatively, Davies [20] has drawn attention to the effect of fenfluramine on the satiety ratio and has argued that the postponement of the onset of further eating following any particular meal is due to a peripheral effect of fenfluramine in delaying gastric emptying. Experiment 3 in the present series showed that 5-HTP produced a noticeable effect on the satiety ratio which just failed to reach statistical significance; this outcome was largely due to the anomalous behaviour of a single animal. Moreover, to the extent to which MK-486 blocked the peripheral effects of 5-HTP it could be argued that this action upon the satiety ratio was not mediated via any peripheral action. However, in considering the mechanisms responsible for changes in meal size and satiety ratio it is necessary to

recognise the possible direct and indirect effects of 5-HTP on peripheral organs. Although MK-486 may have blocked the direct effect of 5-HTP upon sensitive peripheral sites, it is possible that the central action of 5-HTP gave rise to secondary alterations in gastro-intestinal functions. In turn, these alterations may have been sufficient to bring about the observed changes in feeding parameters. Consequently, in discussing the interaction between 5-HTP administration and subsequent adjustments in the pattern of food consumption it seems appropriate to consider separately the primary site of action of the drug and the site of the mechanisms which may finally bring about the alterations in feeding behaviour.

The findings of the present experiments have revealed that pretreatment with MK-486 may bring about a mild antagonism of the effect of 5-HTP on the weight of food consumed over a short period of time by food deprived rats. However, MK-486 failed to block the slowing of the rate of eating of deprived rats produced by 5-HTP—a phenomenon which is characteristically displayed by a number of treatments believed to facilitate serotonergic neurotransmission. Consequently, it seems likely that the weak effect on the anorexic action of 5-HTP presumably brought about by the changes in peripheral metabolism induced by MK-486 is due to an alteration in the number of eating bouts rather than to a facilitation of the local rate of eating. Additionally, MK-486 did not impair the capacity of 5-HTP to reduce the intrameal rate of eating or meal size in free feeding animals. Taken together these data suggest that the major action of 5-HTP on the profile of food consumption is centrally mediated. However, irrespective of the relative contribution of central or peripheral mechanisms, the present experiments have shown that 5-HTP can give rise to alterations in the patterns of feeding behaviour quite similar to those brought about by certain other pharmacological manipulations of serotonin systems. It remains to be revealed whether these behavioural adjustments are mediated by serotonergic mechanisms specifically involved in the control of feeding (e.g. [8,14]) or by systems more generally concerned with behavioural inhibition (e.g. [25]).

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